Current Thinking and Research On In Vitro Only Approaches for Injectable Drug Substance Suspensions-A Scientific Discussion

SBIA 2022: Advancing Generic Drug Development: Translating Science to Approval

Day 1, Session 3: (Simple Injectables)

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Learning objectives

- Identify injectable drug substance suspensions
- Categorize injectable drug substance suspensions into three groups
- Summarize current thinking and research regarding in vitro bioequivalence (BE) approach of each group

Scope of this presentation

- Injectable suspensions are considered complex products, as defined in GDUFA II commitment letter[1].
- Injectable drug substance suspensions discussed in this talk are a complex dosage form, the degree of complexity can be put into three categories.
- FDA is interested in developing a better understanding of the relationship of product critical quality attributes (CQAs) to the in vivo performance, including in vitro in vivo correlation (IVIVC) to support in vitro based approaches.

1. https://www.fda.gov/media/101052/download

Parenteral suspension as a dosage form

- Injectable suspensions are suspension products for parenteral routes of administration: intramuscular (IM), subcutaneous, intra-articular, intravenous (IV), intra-ocular, etc.
- The most common injectable suspensions are drug substance suspensions
  - Particles are made up only of micronized or nanosized drug substance and there are no release modifiers in the solution phase and there are no insoluble excipients in the solution phase.
  - e.g., Kenalog 40 triamcinolone acetonide injectable; injection
- The Orange Book also lists some polymeric microparticles and situ forming implants as suspension; these are not drug substance suspensions
  - e.g., Vivitrol naltrexone for suspension, extended release; intramuscular

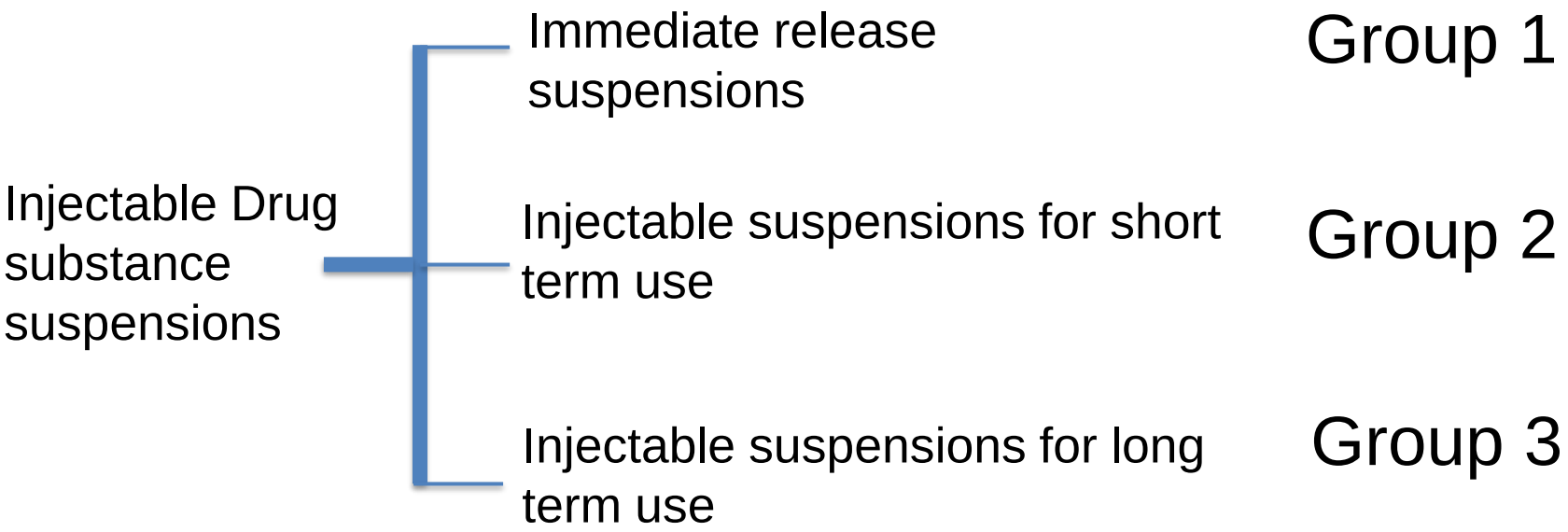
    Perseris Kit risperidone for suspension, extended release; subcutaneous

Injectable drug substance suspensions

- Drug substance suspensions have simpler drug release mechanism than suspension products that contain release controlling excipients
  - Drug substance particles are the only insoluble component in the formulation (or reconstituted formulation)
  - Drug release does not rely on the release controlling excipients
  - Dissolution rate is generally determined by particle size and solubility of the drug substance

$$\frac{dC}{dT} = \frac{D \cdot A}{h \cdot V}(C_s - C_i)$$

Grouping injectable drug substance suspensions



General features of injectable drug substance suspensions

- Drug substance should have low solubility in the dispersing media; may use pro-drug or salt of solvate to reduce solubility
- In general, reducing the drug particle size results in an increased surface area, which leads to an increased dissolution rate
- Stabilizer and/or viscosity agents may be used to induce flocculation and prevent agglomeration/Ostwald ripening
- Lyophilization may be applied for physical stability consideration

BE approaches of injectable drug substance suspensions

- BE studies should be sensitive, accurate, and reproducible
- BE studies with pharmacokinetic (PK) endpoints have been commonly recommended by FDA in product-specific guidances (PSGs)[2] for systemically acting injectable suspensions
- In addition to in vivo BE studies, FDA has recommended in vitro BE studies for some injectable drug substance suspensions

2. https://www.accessdata.fda.gov/scripts/cder/psg/index.cfm

In vitro BE approach

- An in vitro-only BE approach generally relies on totality of evidence
  - When a suspension product is formulated Q1/Q2* the same, there could be differences in the arrangement of matter within the dosage form, which may impact product performance
  - These differences in arrangement of matter may arise from differences in manufacturing, processing, or excipient grade/source
  - These differences can be evaluated by comparative physicochemical tests and in vitro performance test (i.e., in vitro release testing (IVRT))
  - Similarity in physicochemical characteristics and in vitro performance can demonstrate overall product sameness, and thus equivalence

* Q1 (Qualitative sameness) means that the test product uses the same inactive ingredient(s) as the RLD product. Q2 (Quantitative sameness) means that concentrations of the inactive ingredient(s) used in the test product are within ±5% of those used in the RLD product.

Examples of Group 1

NDA #	Drug substance & dosage form	Dosing interval	Indication	Route	Solubility of drug substance
050794	Azacitidine powder	Daily for 7 days (a cycle), repeat cycles every 4 weeks; 4-6 cycles	Treatment of patients with specific FAB myelodysplastic syndrome subtypes	IV, SC	13 mg/mL[1]
210583	Meloxicam solution	Once daily	Management of moderate-to-severe pain	IV	>600 μg/mL in pH 7.5 buffer[2]
205579	Dantrolene sodium for suspension	Single dose; 75 mins prior to surgery	Treatment or prevention of malignant hyperthermia	IV	21 μg/mL in pH 7.4 Tris buffer[3], higher solubility in plasma.

1 Azacitidine Accord EMA assessment report
2 European Journal of Pharmaceutical Sciences 109 (2017) 317-358
3 Talanta, 1998, 35(8): 613-619

Group 1: immediate release injectable suspensions

- Common features of Group 1:
  - Provide immediate systemic availability of suspended drug
    - Rapid dissolution after intravenous (IV) injection (e.g., dantrolene sodium, meloxicam)
    - Or fully dissolved prior to IV injection (e.g., azacytidine has relatively high solubility)
  - Short-dosing interval (e.g., daily) or one-time use
  - Short-term use, not indicated for chronic diseases
- May be feasible to use in vitro BE studies to demonstrate BE
- In vitro BE options are available in PSGs, e.g., dantrolene sodium injection, meloxicam injection

Additional considerations

- For products intended for rapid dissolution after injection, such as dantrolene, the IVRT is aimed to show comparative fast release.
- Discriminative power of IVRT may not be practical for this type of product, thus not necessary.

Examples of Group 2

NDA#	Drug substance & dosage form	Dosing interval	Indication	Route	Solubility of drug substance
011757	Methylprednisolone acetate injectable	Not specified	Anti-inflammatory glucocorticoid	Injection	0.22 mg/mL in water[1]
014901	Triamcinolone acetonide injectable	Not specified	Anti-inflammatory glucocorticoid	Injection (for intramuscular or intra-articular use only)	0.021 mg/mL in water[2]
012041	Triamcinolone acetonide injectable	No specified	Anti-inflammatory glucocorticoid	Injection (for intra-articular or intralesional use only)	0.021 mg/mL in water[2]
022048	Triamcinolone acetonide injectable	Not specified	Ophthalmic diseases, visualization during vitrectomy	Intravitreal	0.021 mg/mL in water[2]
050141	Penicillin G Benzathine injectable	Single injection or 7 days interval for three doses or once a month or biweekly	Treat or prevent infections caused by bacteria	Injection (deep intramuscular injection)	0.2-0.3 mg/mL in water[3]

1 Arch Neurol, 1973, 28: 324-328
2 Journal of Pharmaceutical Sciences, 1973, 62(4): 617-621
3 American Hospital Formulary System, G. McEvoy (Ed.), (2001), pp. 315-346

Group 2: injectable drug substance suspensions for short-term use

- Comment features of Group 2:
  - Micro-sized solid drug particles suspensions
  - Certain level of sustained drug release
  - Dosing interval not be well defined (except penicillin G benzathine); not for long-term use
  - Steroids or antibiotics
- May be feasible to use in vitro BE studies to demonstrate BE
- In vitro BE option or in vivo BE option are recommended in the PSGs, e.g., triamcinolone acetonide injectable injection, methylprednisolone acetate injectable injection, penicillin G benzathine injectable injection

Example: in vitro option in PSG of triamcinolone acetonide injectable; injection

I. In vitro option:

To qualify for the in vitro option for this drug product, all the following criteria should be met:

1. The test and reference listed drug (RLD) formulations are qualitatively (Q1)[1] and quantitatively (Q2)[2] the same (Q1/Q2).
2. Acceptable comparative physicochemical characterizations of the test and the reference standard (RS) products. The comparative study should be performed on a minimum of three exhibit batches of the test product[3] and three batches of the RS product (as available) for all three strengths (10 mg/mL, 40 mg/mL, and 80 mg/mL) and should include:

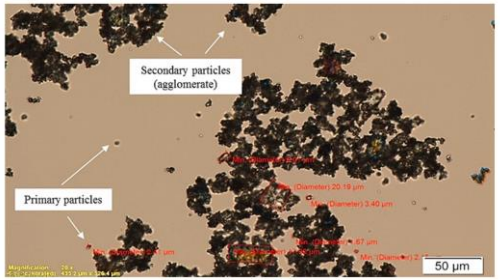
    a. Polymorphic form of triamcinolone acetonide.
    b. Crystalline shape and morphology of triamcinolone acetonide.
    c. Appearance, pH, osmolality, viscosity over a range of shear rates, specific gravity.
    d. Drug particle size and size distribution. The particle size distribution should be compared using population bioequivalence (PBE) (95% upper confidence bound) based on D50 and SPAN [i.e. (D90-D10)/D50)]. The applicant should provide no fewer than ten data sets from three different batches of both the test and RS products for PBE analysis. Full profiles of the particle distribution should also be submitted for all samples tested. Refer to the draft product-specific guidance on *Budesonide, Inhalation; Suspension* for additional information regarding PBE.

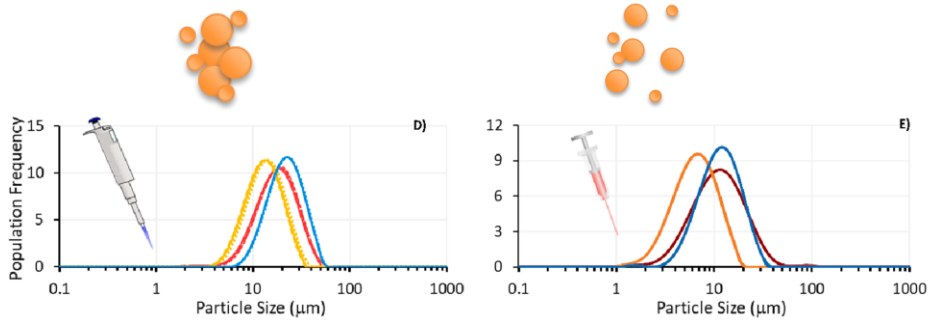
3. Acceptable comparative in vitro drug release of triamcinolone acetonide from the test and RS products for all three strengths (10 mg/mL, 40 mg/mL, and 80 mg/mL). The methodology used for in vitro drug release testing should be able to discriminate the effect of process variability in the production of the test formulation.

https://www.accessdata.fda.gov/drugsatfda_docs/psg/PSG_012041.pdf

GDUFA research: impact of shear-induced deflocculation on drug release

Triamcinolone acetonide injectable suspension



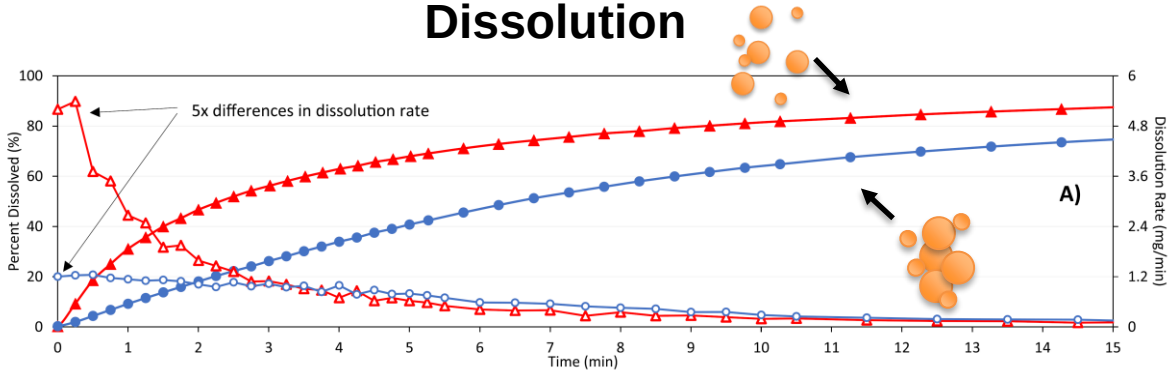


Stirring, sonication, etc. (shear)

Flocculated

Deflocculated

Dissolution



William Smith et al. IJP, 604 (2021) 120767

Examples of Group 3

NDA #	Drug substance & dosage form	Dosing interval	Indication	Route	Solubility of drug substance
202971	Aripiprazole for suspension, extended release;	Monthly	Schizophrenia, bipolar I disorder	IM	~0.010 mg/mL in water[1]
207533	Aripiprazole lauroxil suspension, extended release	Monthly, monthly or every 6 weeks, every 2 month	Schizophrenia	IM	Low (e.g., <10 µg/mL)
022264, 207946, 207946	Paliperidone palmitate suspension, extended release	Monthly, 3 months, 6 months	Schizophrenia, Schizoaffective disorder	IM	Low (e.g., <10 µg/mL)
022173	Olanzapine pamoate suspension, extended release	2 wks, 4 wks	Schizophrenia	IM	0.060 mg/mL in pH 7.68 buffer[2]
212888	Cabotegravir; Rilpivirine suspension, extended release	2 months	HIV-1 infection treatment	IM	0.032 mg/mL[3]; ~0.018 mg/mL[4]
215499	Cabotegravir suspension, extended release	2 months	Reduce the risk of sexually acquired HIV-1 infection	IM	0.032 mg/mL[3]
020246	Medroxyprogesterone acetate injectable	3 months (not for >2 years use)	Prevent pregnancy	IM	

1. Molecular Pharmaceutics 2014, 11, 1739-1749
2. BMS Psychiatry. 2010, 10:45
3. Biomaterial 2018, 151, 53-65
4. Beni-Suef University Journal of Basic and applied sciences, 2015, 71-79

Group 3: Injectable drug substance suspensions for long-term use

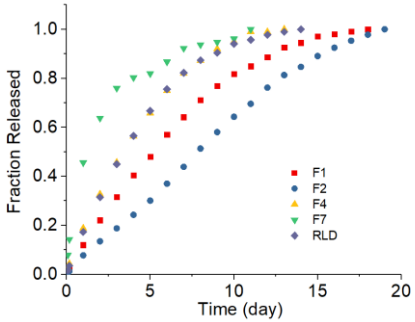
- Common features of Group 3:
  - Nano- to micro-sized solid drug particles for intramuscular injection
  - Extended-release of drug
  - Well defined dosing interval (e.g., weeks to months)
  - Generally, for long-term therapy or chronic diseases treatment (e.g., antipsychotic, HIV treatment or prevention)

Group 3: Injectable drug substance suspensions for long-term use

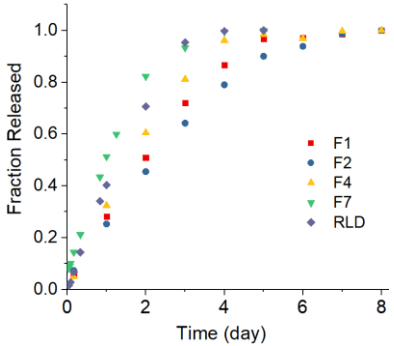
- Posted draft PSGs for drug products in Group 3 recommend in vivo BE studies
- In vitro BE approach may be scientifically feasible, but additional information may be needed to support an in vitro BE approach
  - E.g., PK data or in vitro in vivo correlation (IVIVC) to support the design space of the selected critical quality attributes (CQAs) proposed in the in vitro BE approach

GDUFA research: IVRT method development for LAI and validation with in vivo model

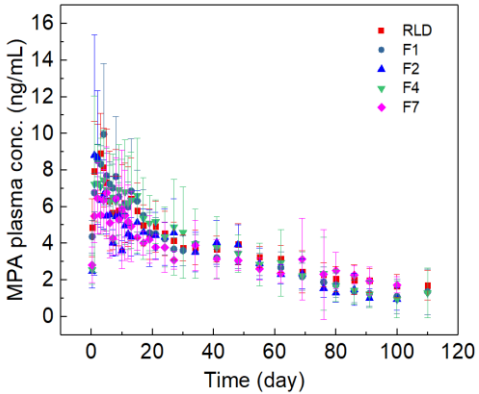
USP apparatus 2
With enhancer cells



USP apparatus 4 with semi solid adaptor



In vivo rabbit model



IVIVC analysis

Model drug: medroxyprogesterone acetate injectable; injection

PI: Dr. Diane Burgess, University of Connecticut (BAA #HHSF223201710135C)

Summary

- Based on dosing interval, indication and therapy duration, etc., injectable drug substance suspensions were roughly categorized into three groups.
  - Group 1: Immediate release suspensions
  - Group 2: Injectable suspensions for short term use
  - Group 3: Injectable suspensions for long term use

Summary (cont.)

- It is strongly recommended that applicants discuss any alternative in vitro BE approach through a pre-ANDA meeting prior to submitting an ANDA.
- For Groups 1 and 2 products:
  - OGD has include in vitro BE option in some PSGs. It may be feasible to use in vitro BE studies to demonstrate BE.
  - Supportive information to support a proposed alternative in vitro BE approach include, but not limited to, whether the proposed formulation is Q1/Q2 the same, justification of the selected CQAs (how the CQAs related to in vivo performance), comparative characterization data, etc.

Summary (cont.)

- Although in vitro BE approach may be scientifically feasible for Group 3 products, additional information may be needed to support an in vitro BE approach, e.g., PK data or IVIVC to support the design space of the selected critical quality attributes
- GDUFA research has helped develop new tools to characterize injectable suspensions to support BE and/or for quality control purpose.

Challenge Question #1

Which of the following bioequivalence approach is currently recommended in the PSG on long-acting systemic injectable suspension that has potential safety concerns?

A. Biowaiver

B. In vitro approach

C. In vivo PK study

D. B & C

Challenge Question #2

True or False? FDA recommends in vitro only BE approach for immediate release suspension products like dantrolene sodium injection in the product specific guidance?

A. True

B. False

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